REMARKS

The present application was originally filed with 13 Claims. In a Supplemental Preliminary Amendment mailed September 21, 2001, Claims 1-6 and 11-13 were cancelled without prejudice and Claims 14-27 were added. Thus, Claims 7-10 and 14-27 were pending. In response to the present Restriction Requirement, the Examiner restricted the Claims into three Groups, with Claims 7-10 and 14-15 in Group I, Claims 7-8 and 14-15 in Group II, and Claims 16-27 in Group III. In a Response filed October 9, 2002, Applicants elected the Claims in Group I with traverse, and cancelled Claims 16-27.

In regard to the Examiner's objections to the Specification, Applicants have amended the Specification to include the additional information related to the applications. In addition, the "R" factor formula, as set forth in priority U.S. Patent Application Serial Number 09/060,872 has been added to the Specification. In addition, the typographical error in Claims 7 and 8 has been corrected. No new matter is added in these amendments.

The Examiner's rejections are addressed in the following order.

1) Claims 8-10 and 14-15 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;

2) Claim 7 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Carr *et al.* (WO 98/52976);

3) Claims 7-10 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Robinson (5,500,362) in light of Carr *et al.* (WO 98/52976);

4) Claims 7-10 stand rejected under 35 U.S.C. §102(b) or (e), as allegedly being anticipated by Rodriguez et al. (EP 699,755 or corresponding U.S. 5,712,120); and

5) Claim 7 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Barstad *et al.* (5,268,454).

1) The Claims are Definite

The Examiner has rejected Claims 8-10 and 14-15 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants appreciate the Examiner's review of the Claims and his suggestions and have amended the Claims to more clearly define the claimed invention. Thus, Applicants respectfully request that this rejection be withdrawn.

2-5) The Claims are Novel

The Examiner has rejected Claim 7 under 35 U.S.C. §102(b) as allegedly being anticipated by Carr *et al.* (WO 98/52976), while Claims 7-10 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Robinson (5,500,362) in light of Carr *et al.* (WO 98/52976), Claims 7-10 stand rejected under 35 U.S.C. §102(b) or (e), as allegedly being anticipated by Rodriguez *et al.* (EP 699,755 or corresponding U.S. 5,712,120), and Claim 7 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Barstad *et al.* (5,268,454).

2) Claim 7 is Novel Over Carr *et al.* (WO 98/52976; Carr *et al.*)

The Examiner argues that Claim 7 is anticipated because Carr *et al.* show "modification of streptokinase by identifying T-cell epitopes therein and then modifying these epitopes by substitution of amino acid residues within these epitopes. See page 4 and 35-38. With these modifications the kinase is less immunogenic." (Office Action, page 3). The Examiner further argues that in "another embodiment Carr discloses the modification of antibodies, such as monoclonal antibodies from a mouse, for use in humans. Within the V-region T-cell epitopes are identified and altered by amino acid substitutions to eliminate these. . . . Carr also discloses that the mouse C-region can be replaced with a corresponding C-region from a human antibody. This C-region from the human source properly constitutes "a corresponding terminal portion of a homolog" of the mouse monoclonal antibody. Thus claim 8 is included in the rejection." (Office Action, pages 3-4). The Examiner also indicates that Claims 9-10 are included "because replacing the whole of a mouse antibody C-region with a human C-region . . . . would be expected to eliminate multiple T-cell epitopes." (Office Action, page 4).

Applicants respectfully submit that Carr *et al.* is **NOT** prior art which is citable against the present application. Carr *et al.* was published on 26 November 1998, while the present application claims priority benefit to US Appln. Ser. No. 09/060,872, filed April 15, 1998. Thus, as the priority application was filed more than seven months BEFORE Carr *et al.* was published as a PCT application. The present application and Claims find support in the originally filed Application Ser. No. 09/060,872 (*See e.g.*, page 5, line 28 through page 7, line 7). Thus, Carr *et al.* is not prior art as to the present application.

3) Claims 7-10 Are Novel Over Robinson (5,500,362; "'362 Patent") in light of Carr *et al.* (WO 98/52976)

The Examiner has rejected Claims 7-10 under 35 U.S.C. §102(a) as allegedly being anticipated by Robinson (5,500,362) in light of Carr *et al.* (WO 98/52976). As indicated above, Carr *et al.* is not properly cited prior art. Thus, these two references cannot be properly combined to reject the present application. As indicated, the '362 Patent "provides a novel approach for the cloning and production of a human/mouse chimeric antibody with specificity to a human B cell surface antigen." (*See*, '362 at col.7, lines 52-54). However, there is no teaching in the '362 Patent of variant of a polypeptide of interest comprising a T-cell epitope, wherein the variant differs from a polypeptide of interest by having an altered T-cell epitope such that the variant and original polypeptide produce a different immunogenic response in an individual, wherein the T-cell epitope is altered by having at least one amino acid substitution, as claimed in the present application. Furthermore, this reference does not teach polypeptides of interest selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines. As this reference does not teach nor suggest the presently claimed invention, Applicants respectfully submit that the '362 Patent does not anticipate the presently claimed invention and request that this rejection be withdrawn.

4) Claims 7-10 Are Novel Over Rodriguez (EP 699,755 or 5,712,120)

The Examiner has rejected Claims 7-10 under 35 U.S.C. §102(b) or (e), as allegedly being anticipated by Rodriguez *et al.* (EP 699,755 or corresponding U.S. 5,712,120). The Examiner argues that "Rodriguez et al's disclosure is similar to that of Carr. That is, T-cell epitopes within the framework segments of the V-region of a rodent antibody are modified by amino acid substitutions to render the V-region, [sic] non-immunogenic in humans. If one thus modifies a V-region rodent, C-region human chimerical antibody (e.g. claims 26-28 of Rodriguez et al. '755) one obtains the product of claim 7, assuming that the chimerical antibody is the 'protein of interest.' Additionally, the chimerical antibody per se may be considered as a modification of a fully rodent antibody (the 'protein of interest'), in which case claims 8-10 are anticipated, as argued supra regarding Robinson et al." (Office Action, page 5).

Applicants must respectfully disagree with the Examiner's arguments. Nonetheless, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended Claims 7 and 8 to recite that the polypeptide of interest is selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines. There is support throughout the Specification as

filed for these polypeptides (*See e.g.*, page 4, lines 23-25; and originally filed Claim 4). As Rodriguez does not teach nor suggest altering the epitopes of any of these polypeptides of interest, Applicants respectfully submit that the Claims are not anticipated by Rodriguez and request that this rejection be withdrawn.

5) Claim 7 is Novel Over Barstad *et al.*

The Examiner has rejected Claim 7 under 35 U.S.C. §102(b) as allegedly being anticipated by Barstad *et al.* (5,268,454). In particular, the Examiner argues that "Barstad et al teach analogs of a polypeptide immunogen which retains B-cell epitopes but which lacks T-cell epitopes. The latter are eliminated by chemical derivitization or are partially or completely deleted from the sequence. . . . It is to be noted that though Barstad et al teach the conjugation of the altered, T-cell epitope efficient [sic[polypeptide to a nonimmunogenic carrier polymer for the purpose of inducing B-cell energy [sic] . . . the altered polypeptide, never the less, existed as a composition, per se, prior to its conjugation."

Applicants must respectfully disagree with the Examiner's arguments. Contrary to Barstad *et al.*, the present invention recites a polypeptide of interest and variant polypeptide of interest that *comprise* a T-cell epitope, albeit the variant polypeptide has an altered T-cell epitope. Indeed, Barstad *et al.* teach away from the presently claimed invention, as their invention involves immunogens that LACK T-cell epitopes. The present invention requires the presence of T-cell epitopes. Thus, Applicants respectfully submit that contrary to the Examiner's assertions, the presently claimed invention is not anticipated by Barstad *et al.*, and request that this rejection be withdrawn.

CONCLUSION

In light of the above remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully

requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

Date: April 7, 2003

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APPENDIX I
MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS AND REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b), as well as a marked-up version of the claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Underlining denotes added text while bracketing denotes deleted text.

IN THE SPECIFICATION:

On page 1, under "CROSS-REFERENCE TO RELATED APPLICATIONS" please delete

[This application is a continuation in part of USSN 09/677,822, filed October 2, 2000, which is a continuation-in-part of USSN 09/500,135, filed April 2, 2000, which is a continuation in part of USSN 09/060,872, filed on April 15, 1998, all of which are incorporated by reference in their entirety.]

and insert the following:

The present application is a Continuation-in-Part of U.S. Patent Application Serial Number 09/677,822, filed October 2, 2000, which is a Continuation-in-Part of U.S. Patent Application Serial No. 09/500,135, filed February 8, 2000, which is a Continuation-in-Part of U.S. Patent Application Serial Number 09/060,872, filed April 15, 1998. The present application also claims priority to U.S. Patent Application Serial Nos. 09/255,502 (now U.S. Patent No. 6,218,165, issued April 17, 2001), 09/255,505 (now abandoned), and 09/255,501, all of which were filed on February 23, 1999, and are Divisional applications of U.S. Patent Application Serial No. 09/060,872. All of these applications are incorporated by reference in their entirety.

IN THE CLAIMS:

7. (Twice amended) A variant of a polypeptide of interest comprising a T-cell epitope, wherein said variant differs from said polypeptide of interest by having an altered T-cell epitope such that said variant and said polypeptide produce a different immunogenic response in an individual, wherein said T-cell epitope is altered by having at least one amino acid substitution, and wherein said polypeptid of interest is selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines.

8. (Twice amended) A variant of a polypeptide of interest comprising a T-cell epitope, wherein said variant differs from said polypeptide of interest by having an altered T-cell epitope such that said variant and said polypeptide produce a different immunogenic response in an individual, wherein said T-cell epitope is altered by having a terminal portion of said polypeptide of interest comprising said T-cell epitope replaced with a corresponding terminal portion of a homolog of said polypeptide of interest wherein said homolog does not comprise a T-cell epitope identical to said replaced epitope, and wherein said polypeptide of interest is selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines.

9. (Amended) The variant of claim 8 wherein said variant comprises at least one less T-cell epitope than said polypeptide of interest [and said homolog combined].

10. (Amended) The variant of claim 8 wherein said variant comprises at least two less T-cell epitopes than said polypeptide of interest [and said homolog combined].

APPENDIX II

CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

The following is a list of the Claims as they would appear following entry of this amendment.

7. (Twice amended) A variant of a polypeptide of interest comprising a T-cell epitope, wherein said variant differs from said polypeptide of interest by having an altered T-cell epitope such that said variant and said polypeptide produce a different immunogenic response in an individual, wherein said T-cell epitope is altered by having at least one amino acid substitution, and wherein said polypeptide of interest is selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines.

8. (Twice amended) A variant of a polypeptide of interest comprising a T-cell epitope, wherein said variant differs from said polypeptide of interest by having an altered T-cell epitope such that said variant and said polypeptide produce a different immunogenic response in an individual, wherein said T-cell epitope is altered by having a terminal portion of said polypeptide of interest comprising said T-cell epitope replaced with a corresponding terminal portion of a homolog of said polypeptide of interest wherein said homolog does not comprise a T-cell epitope identical to said replaced epitope, and wherein said polypeptide of interest is selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines.

9. (Amended) The variant of claim 8 wherein said variant comprises at least one less T-cell epitope than said polypeptide of interest.

10. (Amended) The variant of claim 8 wherein said variant comprises at least two less T-cell epitopes than said polypeptide of interest.

14. The variant of claim 8, wherein the polypeptide of interest and the homolog of said polypeptide are proteases.

15. The variant of claim 14, wherein said protease is a subtilisin.